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The Efficacy of Microcurrent Transcutaneous Electric Nerve Stimulation as Compared to Placebo in Reducing Pain Caused by Diabetic Neuropathy: A Systematic Review

Joe Russell

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Abstract

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Method: An exhaustive literature search using Medline, Cinahl, Evidence-Based Medicine Reviews Multifile, and Google Scholar was performed. The following search terms with common synonyms were used: *microcurrent* and *diabetic neuropathy*. Only randomized controlled trials were used.

Results: Three articles were found that addressed the question of interest and met all eligibility criteria. Two of the three studies showed that microcurrent therapy and placebo significantly reduced pain but one was not more efficacious than the other. The other study found microcurrent therapy was more efficacious than placebo. All studies received a GRADE quality of evidence rating of low.

Conclusion: At this time there is not enough high quality evidence to say with any certainty that microcurrent therapy is more efficacious than placebo in reducing pain caused by diabetic neuropathy. The three RCTs that have been performed to date, have been small and have conflicting results. The results do indicate a large placebo effect which should not be discounted when considering the utility of microcurrent therapy.

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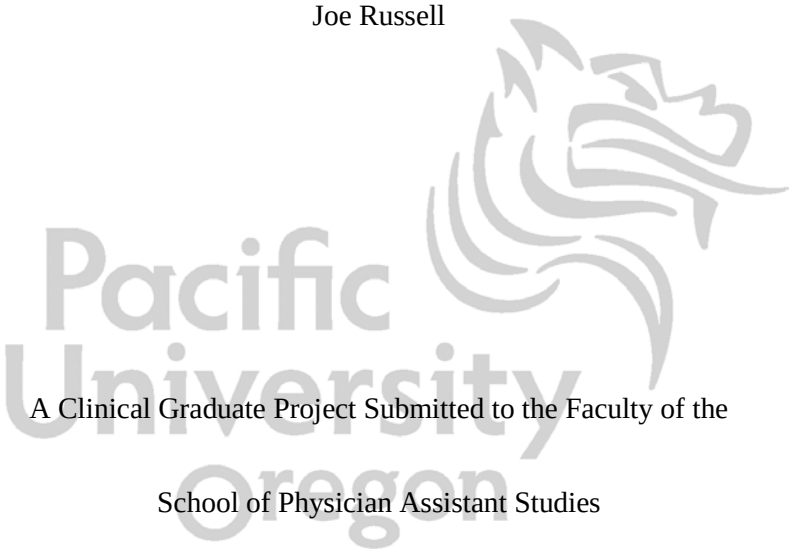

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Faculty Advisor: Dr. Rosenow

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Biography

Joe Russell is a native of Oregon where he majored in Biology at Oregon State University. He worked as an EMT-Basic in Eugene, Oregon before starting PA school at Pacific University.

Abstract

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To *my friends and family*: Thank you for supporting me in so many ways through the years as I pursued my dreams. I could never have come this far without your help and encouragement.

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List of Abbreviations

MTENS……Microcurrent Transcutaneous Electric Nerve Stimulation

NPS……...Neuropathic Pain Scale

TENS…….……..Transcutaneous Electric Nerve Stimlation

VAS.....Visual Analog Scale

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BACKGROUND

Pain caused by diabetic neuropathy is a common complication in diabetic patients. Between 1980 and 2010 the CDC reports the number of people with diabetes in the U.S. had increased from 5.6 million to 20.9 million. Among these individuals the rate of neuropathy is steadily increasing.[1] Pharmacological treatments have had some success in treating pain caused by diabetic neuropathy[2] but because of side effects non-pharmacological treatments are appealing to both patients and healthcare providers. Transcutaneous electric nerve stimulation (TENS) is one such treatment option. More recently a different form of TENS using microamperes instead of milliamperes called microcurrent therapy or microcurrent transcutaneous electric nerve stimulation (MTENS) has re-emerged since it fell out of favor with the AMA in the early part of the 20th century. The lack of harmful side effects associated with MTENS make it a potentially important option for patients who struggle with chronic pain caused by diabetic neuropathy and either do not respond to other treatments or do not wish to use pharmacologic treatment. One small study[3] showed that microccurrent therapy reduced the pain of diabetic neuropathy significantly, but in this study there was no control group to use as a comparison. Researchers have demonstrated that microcurrent therapy can increase ATP generation and protein synthesis in rats which may have important implications for wound healing.[4] Its use in treating other ailments such as tendinitis has

also been explored.[5] Microcurrent therapy is currently being used as an alternative treatment option for painful diabetic neuropathy, yet little research has been done to date on the efficacy of this treatment option in randomized controlled trials as compared to placebo. This systematic review was performed because there is no general consensus regarding the efficacy of this appealing treatment option for painful diabetic neuropathy.

METHODS

An exhaustive literature search using Medline, Cinahl, Evidence-Based Medicine Reviews Multifile, and Google Scholar was performed. The search terms used in all databases were *microcurrent* and *diabetic neuropathy*. In addition *electrical stimulation*, *microampere*, and *Neuropathic Pain Scale* were used to broaden the search. The limits *English Language*, *Humans*, and *exclude Medline records* were applied, when applicable, to help focus the search. Articles were screened by title, abstract, and/or review of the full text for relevance. The references of relevant articles were also reviewed for eligible studies.

Eligibility Criteria

There were 5 inclusion criteria for the search: 1) The study must be a randomized controlled trial (RCT); 2) patients must have been adults who were diagnosed with diabetic peripheral neuropathy; 3) the electrotherapy used microamperes; 4) a control group was used; 5) pain was used as an endpoint.

Exclusion criteria included: 1) Electrical stimulation of the central nervous system was used; 2) Concomitant therapies were used along with microcurrent therapy in such a

way that attributing the results to microcurrent therapy alone would be difficult; 3) Electrical stimulation used the traditional milliampere intensity setting.

Literature appraisal and evidence grading—A thorough appraisal was done to evaluate each article for individual strengths and weaknesses using a form which addressed validity, magnitude and precision of results, and implications for clinicians and researchers. Each article was given a final quality rating according to the GRADE system.[6] This process is described in the discussion section and summarized in Tables I and II.

RESULTS

A total of 585 studies were screened for relevance. Three articles[7-9] were found that met the inclusion and exclusion criteria. The first article by Gossrau et al[7] is titled *Microcurrent transcutaneous electric nerve stimulation in painful diabetic neuropathy: A randomized placebo-controlled study* and was published in 2011. This study was a small, single blinded, RCT that administered 30-40 microamperes transcutaneously to the legs of 21 patients 3 times a week for 30 minutes a day over a 4 week period. Randomization was not described. The smoking status of participants was not reported. All procedures were exactly duplicated for the 19 patients who constituted the control group except the leads were not connected to the machine. Multiple subjective outcomes were recorded but the study defined a successful treatment as at least a 30% reduction in Neuropathic Pain Score (NPS). All outcomes were measured at the start of the trial, after 4 weeks of

therapy, and 4 weeks after therapy was completed. No significant difference was found between the treatment group and the control group in any of the outcomes measured. No adverse side-effects were noted in any of the patients although in both groups some patients reported a pleasant warm sensation in their legs. Both groups contained patients who responded to their respective treatments. A responder was defined as a patient who experienced a 30% or greater reduction in their NPS. There were more responders (10/19) in the control group than there were in the treatment group (6/21); but this difference was not statistically significant. The authors concluded therefore, that according to their results mirocurrent therapy was not superior to placebo for reducing pain caused by diabetic neuropathy.[7]

The second study found was conducted by Rae et al[8] called *The effect of microcurrent electrical stimulation on the foot blood circulation and pain of diabetic neuropathy* and was also published in 2011. This was a small RCT that compared microcurrent therapy and walking exercises with walking exercises alone. The treatment used was pulsed at "less than 300 microamperes" via special shoes that the patients used while doing walking exercises. These exercises were done every day for 4 weeks in both groups. Shoes were similar in shape but no current was administered in the placebo group. Pain and foot blood circulation values for the two groups were recorded at the beginning of the 4 week period and then once at the end. The authors claim the study was double blinded but they failed to explain how the treatment providers were blinded. They specify that "…subjects were randomly arranged into an experimental and control group to perform a double blind study". The process of randomization was not described. This study reported a statistically significant difference between the treatment and control

groups; with the treatment group showing greater reduction in pain. Pain was measured on a 10 point visual analog scale (VAS). The experimental group's average VAS for pain at the start of the study was 6.69 +/- 2.00. After the study it was 3.25+/- 1.73. The control group's average VAS for pain was 7.31 +/- 1.80 at the start of the study and 6.85 +/- 2.11 after the study. Foot blood circulation was also measured as a primary endpoint and showed significant improvement in the treatment group.[8]

The last study by Oyibo et al[9] titled *Electrical Stimulation therapy through stocking electrodes for painful diabetic neuropathy: a double blind, controlled crossover study* was published in 2003. In this study 30 patients were randomized to have either 50 microamperes administered each night via stocking electrodes for 6 weeks or a negligible 5 microamperes administered via identical stockings which acted as the control. Randomization was not described. The 5 micro amps were used so the lights on the machine would be lit and appear identical to the machines administering the experimental dose. After the first 6 weeks all the patients entered a 4 week non-treatment phase where no one wore the stocking electrodes. After the non-treatment phase the patients crossed over to have either the control therapy or the treatment therapy for another 6 weeks. Sixteen patients did not complete the first 6 week phase. The reasons for withdrawals between the two groups were similar. "Intolerable or inconvenient" and "unhelpful" were the most common causes of patient withdrawals. In the control group there were 2 patients who dropped out because of dermatitis. The remaining 14 patients who completed the study were used in the results. Both pain and sleep disturbance were used as end points. The treatment phase and the control phase demonstrated significant reductions in pain; a 40.1% reduction and a 49.2% reduction, respectively. Based on

these results the authors concluded that there was no evidence to support microcurrent therapy as being more effective than placebo for reducing pain caused by diabetic neuropathy.[9]

DISCUSSION

The available research on the efficacy of microcurrent therapy in reducing pain caused by diabetic neuropathy as compared to placebo, is sparse and of low quality (Table I), indicating further research is likely to have a large impact on our estimate of the effect of microcurrent therapy for painful diabetic neuropathy.

Two of the three studies[7,9] showed that microcurrent therapy and placebo significantly reduced pain but one was not more efficacious than the other. The other study[8] found microcurrent therapy was more efficacious than placebo (Table II). With only three low quality studies with conflicting results the question at hand cannot be answered with any degree of certainty. The results do indicate a large placebo effect which should not be discounted when considering the utility of microcurrent therapy.

All studies started the GRADE evaluation with a presumptive rating of high because they were all randomized controlled trials. Certain limitations were common to all three studies. They all had small population sizes and lacked solid information on confidence intervals or had large margins of error. Therefore, all studies were downgraded one level for imprecise and underpowered results. Moreover, all of the studies recorded pain which is a subjective outcome. Subjective outcomes per se, increase the risk of bias. Because pain is an important outcome for patients, no downgrade was

made to any study based on its use as an outcome. Downgrades were made for inadequate blinding and non-specific methods of collecting the subjective data. The process of randomization is not described in any of the studies. While this information would have been appreciated, no downgrades were made based on this shortcoming alone.

In the study by Gossrau et al[7] no significant difference between treatment and control was demonstrated. This study was only single blinded and there was not enough detail describing the process by which the authors collected the subjective data. The questionnaires may have been asked by the authors who would have known which treatment each patient received. Due to this increased risk of bias the article was downgraded one level for weakness in methodology. The trial was not stopped early and patients were analyzed in the groups to which they were randomized. No downgrade was made based on inconsistencies. Although the smoking status of the patients in each group is unknown the groups appeared to be similar with respect to other known prognostic factors. Next, the study was downgraded another level of evidence for being underpowered due to a small sample size of 40 and imprecision because no confidence intervals were given. The study started with 41 patients and the results accounted for 40. This was either a glaring error in simple mathematics or a failure to follow-up with the patient without explanation. A single patient would not have changed the results of the study so no downgrade was made based on this weakness. No publication bias was detected. Ultimately the final GRADE of the evidence for this study was deemed to be low.

In the study by Rae et al[8] microcurrent therapy was found to be significantly more efficacious than the control in reducing pain caused by diabetic neuropathy. Thirty two subjects began the study and 29 completed it. The 3 that did not, were dropped from the study because they failed to continue their daily exercises. No crossover occurred. Patients were analyzed in the groups to which they were randomized. The study was not downgraded for methodology despite there being some ambiguity regarding the method the authors used to blind the providers in order to make the study double blinded. While it would have been nice to know how that was done it is not reason enough to downgrade the evidence rating. However, there were some significant issues identified in the article. The control and treatment groups may not have been similar with respect to prognostic factors. The study only takes into account the age, sex, height and weight. There are some confounding variables that might significantly skew the results. For example, it is not known how long each person had diabetes. In theory, the control group could have had diabetes for much longer on average, which would mean that the extent of the vascular damage, and therefore nerve damage would be far greater in the control group than the experimental group. With such a small sample size it would not take many patients in the control group having diabetes for significantly longer than the treatment patients to potentially affect the results. This could have affected both the blood circulation and pain intensity. Age plays a similar role. The average age of those in the control group is greater than that of those in the experimental group (70.38 and 67.88 years, respectively). Logically the more time the vascular system is insulted, the more extensive the damage. While the ages may not be significantly different it could tilt the outcomes in favor of the experimental group. Smoking incidences in the two groups is not addressed. Smoking is a

well known and important risk factor in the development of peripheral vascular disease. There were a significantly greater proportion of females in the experimental group. Men tend to have a higher incidence of vascular disease than women which could have been an important difference between the two groups but the authors do not address it. Taken together the differences between the treatment and control groups could have been enough to distort the results in favor of microcurrent therapy. The potential prognostic differences represent an important inconsistency and so the study was downgraded one level. The study was further downgraded for having a small sample size (n=29) which under-powers the results as well as rendering imprecise results. The experimental group's average pain at the start of the study was 6.69 +/- 2.00 and after the treatment it was 3.25+/- 1.73. With error margins this wide, which also overlap, it is difficult to have confidence that there was a significant change. The error margins for the control group were even wider which means the opposite could be true for the control group. One cannot be sure that the actual difference wasn't significant in the control group. No publication bias was detected. The final GRADE of the evidence for this article is low. Overall the study does attempt to answer the key question but the limitations of the study provide little confidence in the results. A larger study with a more robust list of prognostic factors would help to ensure the treatment and control groups are similar, add power to the study, and give a more accurate estimate of the size of the effect that microcurrent has on pain caused by diabetic neuropathy.

The article by Oyibo et al[9] used overnight stocking electrodes to administer the microcurrent therapy or placebo therapy. They found both therapies significantly reduced pain, and both groups saw a similar reduction in the pain level. The study was a

randomized, double blinded, placebo controlled crossover study. Overall the methodology was sound, except the design allowed for significant non-compliance which warranted a downgrade. Out of a possible 336 hours, the patients who received active treatment only wore the stockings for 228 hours and the control group wore them for 248 hours. This means patients only wore the stockings slightly over 2/3 of the time requested. The other two studies ensured that all patients received the assigned treatment every time. No carryover effects could be found which would support the idea that the study designers successfully used the 4 week non-treatment phase to separate the two 6 week placebo and treatment phases. No downgrade was made for inconsistencies. Due to a small sample size (n=14) and for imprecision as demonstrated by the overlapping confidence intervals the study was downgraded another level. The overall GRADE level of this study was low. It is important to note the withdrawal rate associated with this overnight treatment. It does not compromise the quality of the evidence but it does have important clinical implications. In this study over half of the patients who started the study dropped out (16/30). The reason for withdrawals between the two groups were similar. “Intolerable or inconvenient “ and “unhelpful” were the most common causes of patients withdrawal. The study did not differentiate the intolerable withdrawals from the inconvenient withdrawals, which would have been relevant information for providers. Using stockings while sleeping at night would be an inconvenience to patients, but patients who have hyperesthesia type diabetic neuropathy would certainly consider this form of treatment intolerable. In the control group, there were 2 patients who dropped out because of dermatitis. The dermatitis is a significant concern because diabetic patients are

more prone to infection. Any breakdown in the skin due to chronic irritation or scratching would seem to present an unacceptable risk.

CONCLUSION

At this time there is not enough high quality evidence to say with any certainty that microcurrent therapy is more efficacious than placebo. The three RCTs[7-9] that have been performed to date, have been small and have conflicting results. The two studies by Gossrau et al[7] and Oyibo et al[9], that were given GRADE ratings of low, found no difference between microcurrent therapy and placebo therapy but found both treatments significantly reduced pain caused by diabetic neuropathy. The study by Rae et al[8] found that microcurrent therapy reduced pain significantly more than placebo but it was also given a GRADE rating of low.

Implications for Practice

There is currently no good evidence to show that microcurrent therapy is more effective at reducing pain caused by diabetic neuropathy than placebo. That being said, there are virtually no adverse side effects associated with microcurrent therapy. In the studies reviewed in this analysis most patients received significant benefit from using microcurrent therapy and placebo therapy. The value of this perceived affect should not be discounted, particularly in patients who are resistant to other treatments or who suffer severe side effects from medications.

Implications for Research

Microcurrent therapy is imperceptible to humans because it cannot cause nerves to fire or muscles to contract. The fact that microcurrent therapy is indistinguishable from a placebo treatment makes it an excellent candidate for large RCTs which need to be performed before its efficacy can be determined with any certainty. A large well designed RCT would carry considerable weight given the small number of low quality studies that have been performed to date.

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Table I. Characteristics of Reviewed Studies

Study	Study Design	Sample size	Randomization	Concealment	Follow-up	Quality of Evidence (GRADE)
Gossrau et al[7]	Randomized controlled trial	n=41	Adequate, but process not described	Single blinded	8 weeks 1 lost to follow-up	Low - downgraded for lack of concealment and sparse/imprecise data
Rae et al[8]	Randomized controlled trial	n=29	Adequate, but process not described	Double blinded	4 weeks Complete	Low - downgraded for important inconsistencies and sparse/imprecise data
Oyido et al[9]	Randomized controlled trial crossover	n=14	Adequate, but process not described	Double blinded	16 weeks Complete	Low – downgraded for weakness in methodology and sparse/imprecise data

Table II. Summary of Findings

Study	Treatment	Outcome	Treatment Results	Control Results	Significant difference between MTENS and placebo found?
Gossrau et al[7]	30 min. in office microcurrent on legs 3x/week for 4 weeks	Responder = 30% reduction in NPS* sum	6/21* were responders	10/19* were responders	No
Rae et al[8]	Microcurrent administered via shoe while walking 1 hr/day x 4 weeks	Pain reduction as rated on VAS	3.44±2.16	0.46±2.47	Yes
Oyibo et al[9]	Overnight microcurrent via stocking electrodes nightly for 6 weeks	Pain as rated on VAS	Tx Initial Pain = 6.2 (3.9-8.4) Tx End Pain = 3.1 (1.0-5.1)	Control Initial Pain = 7.1 (5.6-8.7) Control End Pain =3.6 (1.8-6.0)	No

* P>0.09, no confidence intervals given